1: Biochim Biophys Acta. 1990 Jun 27;1025(2):143-51.

Characterization of liposomal systems containing doxorubicin entrapped in response to pH gradients.

Mayer LD, Tai LC, Bally MB, Mitilenes GN, Ginsberg RS, Cullis PR.

Department of Biochemistry, Faculty of Medicine, University of British Columbia, Vancouver, Canada.

Studies from this laboratory (Mayer et al. (1986) Biochim. Biophys. Acta 857, 123-126) have shown that doxorubicin can be accumulated into liposomal systems in response to transmembrane pH gradients (inside acidic). Here, detailed characterizations of the drug uptake and retention properties of these systems are performed. It is shown that for egg phosphatidylcholine (EPC) vesicles (mean diameter of 170 nm) exhibiting transmembrane pH gradients (inside acidic) doxorubicin can be sequestered into the interior aqueous compartment to achieve drug trapping efficiencies in excess of 98% and drug-to-lipid ratios of 0.36:1 (mol/mol). Drug-to-lipid ratios as high as 1.7:1 (mol/mol) can be obtained under appropriate conditions. Lower drug-to-lipid ratios are required to achieve trapping efficiencies in excess of 98% for smaller (less than or equal to 100 nm) systems. Doxorubicin trapping efficiencies and uptake capacities are related ito maintenance of the transmembrane pH gradient during encapsulation as well as the interaction between doxorubicin and entrapped citrate. This citrate-doxorubicin interaction increases drug uptake levels above those predicted by the Henderson-Hasselbach relationship. Increased drug-to-lipid ratios and trapping efficiencies are observed for higher interior buffering capacities. Retention of a large transmembrane pH gradient (greater than 2 units) after entrapment reduces the rate of drug leakage from the liposomes. For example, EPC/cholesterol (55:45, mol/mol) liposomal doxorubicin systems can be achieved which released less than 5% of encapsulated doxorubicin (drug-to-lipid molar ratio = 0.33:1) over 24 h at 37 degrees C. This pH gradient-dependent encapsulation technique is extremely versatile, and well characterized liposomal doxorubicin preparations can be generated to exhibit a wide range of properties such as vesicle size, lipid composition, drug-to-lipid ratio and drug release kinetics. This entrapment procedure therefore appears well suited for use in therapeutic applications. Finally, a rapid colorimetric test for determining the amount of unencapsulated doxorubicin in liposomal systems is described.

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the minimum allowed and try again.  Enter HELP SFIELDS to
to find the minimum stem length for left truncation in
the requested search field.

=> s (glycoprotein? (N) (a1 or ?1))
'?1' NOT LONG ENOUGH FOR LEFT TRUNCATION
You have entered a truncated stem whose length is less than
the minimum allowed for left truncation in the requested
search field.  You may increase the length of the stem to
the minimum allowed and try again.  Enter HELP SFIELDS to
to find the minimum stem length for left truncation in
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=> s (glycoprotein? (N) (a1 or alpha1))
L1          519 (GLYCOPROTEIN? (N) (A1 OR ALPHA1))

=> s l1 and desialyated
L2            0 L1 AND DESIALYATED

=> s desialyated
L3           83 DESIALYATED

=> s liposom?
L4       146442 LIPOSOM?

=> s l4 (5n) target?
L5         4859 L4 (5N) TARGET?

=> s l5 and l1
L6            0 L5 AND L1

=> d his

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     FILE 'MEDLINE, BIOSIS, EMBASE, CA, SCISEARCH' ENTERED AT 13:42:09 ON 24
     NOV 2003
L1           519 S (GLYCOPROTEIN? (N) (A1 OR ALPHA1))
L2             0 S L1 AND DESIALYATED
L3            83 S DESIALYATED
L4        146442 S LIPOSOM?
L5          4859 S L4 (5N) TARGET?
L6             0 S L5 AND L1

=> s l4 (3n) (attach? or conjugat? or affix? or bind? or bound? or bond? or embedd?)
L7          9152 L4 (3N) (ATTACH? OR CONJUGAT? OR AFFIX? OR BIND? OR BOUND? OR
                 BOND? OR EMBEDD?)

=> s l1 and l7
L8             0 L1 AND L7

=> s (glycoprotein?)
L9        542571 (GLYCOPROTEIN?)

=> s l7 and l9
L10          657 L7 AND L9

=> s l10 and (liposom? (5n) (target or direct?)
UNMATCHED LEFT PARENTHESIS 'AND (LIPOSOM?'
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=> s l10 and (liposom? (5n) (target or direct?))
L11           64 L10 AND (LIPOSOM? (5N) (TARGET OR DIRECT?))

=> dup rem l11
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L12           30 DUP REM L11 (34 DUPLICATES REMOVED)

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L13           26 L12 AND PY<=2001

=> d l13 1-26 ibib abs

L13  ANSWER 1 OF 26      MEDLINE on STN
ACCESSION NUMBER:    2000237074      MEDLINE
DOCUMENT NUMBER:     20237074   PubMed ID: 10772897
TITLE:               Targeting of liposomes carrying recombinant fragments of
                     platelet membrane glycoprotein Ibalpha to
                     immobilized von Willebrand factor under flow conditions.
AUTHOR:              Nishiya T; Murata M; Handa M; Ikeda Y
CORPORATE SOURCE:    Department of Internal Medicine, Keio University, Tokyo,
                     160-8582, Japan.. nishiya@med.keio.ac.jp
SOURCE:              BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS,
                     (2000 Apr 21) 270 (3) 755-60.
                     Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200005
ENTRY DATE:          Entered STN: 20000606
                     Last Updated on STN: 20000606
                     Entered Medline: 20000522
AB   Liposomes with covalently bound recombinant fragments
     of platelet membrane glycoprotein Ibalpha that retain the von
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Willebrand factor (vWf)-**binding** function (rGPIbalpha-**liposomes**) were prepared. Their interactions with an immobilized vWf surface under flow conditions were evaluated with a recirculating flow chamber, mounted on an epifluorescence microscope, which allows real-time visualization of fluorescence-labeled liposomes interacting with the surface. The interaction of rGPIbalpha-**liposomes** with the vWf surface was **directly** related to shear rate. At high densities of rGPIbalpha and vWf, rGPIbalpha-liposomes establishing contact with the vWf surface exhibited continuous displacement with decreased velocity relative to the hydrodynamic flow, depending on receptor density and matrix concentration. At lower densities of rGPIbalpha and vWf, rGPIbalpha-liposomes stopped only transiently, in the millisecond range, on the surface. This is the first study to demonstrate that the targeting of rGPIbalpha-liposomes is specific to the vWf surface under flow conditions.

L13 ANSWER 2 OF 26 MEDLINE on STN
ACCESSION NUMBER: 1999412365 MEDLINE
DOCUMENT NUMBER: 99412365 PubMed ID: 10482600
TITLE: Low-pH-dependent fusion of Sindbis virus with receptor-free cholesterol- and sphingolipid-containing liposomes.
AUTHOR: Smit J M; Bittman R; Wilschut J
CORPORATE SOURCE: University of Groningen, Department of Physiological Chemistry, 9713 AV Groningen, The Netherlands.
CONTRACT NUMBER: HL 16660 (NHLBI)
SOURCE: JOURNAL OF VIROLOGY, **(1999 Oct)** 73 (10) 8476-84.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991012

AB There is controversy as to whether the cell entry mechanism of Sindbis virus (SIN) involves direct fusion of the viral envelope with the plasma membrane at neutral pH or uptake by receptor-mediated endocytosis and subsequent low-pH-induced fusion from within acidic endosomes. Here, we studied the membrane fusion activity of SIN in a liposomal model system. Fusion was followed fluorometrically by monitoring the dilution of pyrene-labeled lipids from biosynthetically labeled virus into unlabeled liposomes or from labeled liposomes into unlabeled virus. Fusion was also assessed on the basis of degradation of the viral core protein by trypsin encapsulated in the liposomes. SIN fused efficiently with receptor-free liposomes, consisting of phospholipids and cholesterol, indicating that receptor interaction is not a mechanistic requirement for fusion of the virus. Fusion was optimal at pH 5.0, with a threshold at pH 6.0, and undetectable at neutral pH, supporting a cell entry mechanism of SIN involving fusion from within acidic endosomes. Under optimal conditions, 60 to 85% of the virus fused, depending on the assay used, corresponding to all of the virus **bound** to the **liposomes** as assessed in a **direct** binding assay. Preincubation of the virus alone at pH 5.0 resulted in a rapid loss of fusion capacity. Fusion of SIN required the presence of both cholesterol and sphingolipid in the **target liposomes**, cholesterol being primarily involved in low-pH-induced virus-**liposome binding** and the sphingolipid catalyzing the fusion process itself. Under low-pH conditions, the E2/E1 heterodimeric envelope **glycoprotein** of the virus dissociated, with formation of a trypsin-resistant E1 homotrimer, which kinetically preceded the fusion reaction, thus suggesting that the E1 trimer represents the fusion-active conformation of the viral spike.

L13 ANSWER 3 OF 26 MEDLINE on STN
ACCESSION NUMBER: 1999263169 MEDLINE
DOCUMENT NUMBER: 99263169 PubMed ID: 10329552
TITLE: Membrane fusion by surrogate receptor-bound influenza haemagglutinin.
AUTHOR: Millar B M; Calder L J; Skehel J J; Wiley D C
CORPORATE SOURCE: Division of Virology, National Institute for Medical Research, Mill Hill, London, The Ridgeway, NW7 1AA, United Kingdom.
SOURCE: VIROLOGY, **(1999 May 10)** 257 (2) 415-23.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 19990628
Entered Medline: 19990615

AB In influenza infections, haemagglutinin (HA) mediates the fusion of virus and cellular membranes at endosomal pH, between pH 5 and 6. In vitro, when reconstituted into virosomes, efficient fusion requires target membranes to contain sialic acid receptors or receptor analogues. In the experiments reported, lipid-associated anti-HA monoclonal Fab' fragments were used as surrogate receptors to investigate the fusion capacity of receptor-bound HA compared with unbound HA. The conclusions are drawn, in contrast to those from previous studies, that bound HA can mediate fusion and that fusion mainly involves **bound** HA when the **liposome targets** are densely packed with surrogate receptors.

L13 ANSWER 4 OF 26 MEDLINE on STN
ACCESSION NUMBER: 1998151556 MEDLINE
DOCUMENT NUMBER: 98151556 PubMed ID: 9482929
TITLE: Receptor-triggered membrane association of a model retroviral **glycoprotein**.
AUTHOR: Damico R L; Crane J; Bates P
CORPORATE SOURCE: Department of Microbiology, Graduate Program in Cellular and Molecular Biology, University of Pennsylvania, School of Medicine, 3610 Hamilton Walk, Philadelphia, PA 19104-6076, USA.
CONTRACT NUMBER: CA63531 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1998 Mar 3)** 95 (5) 2580-5.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980416
Last Updated on STN: 19980416
Entered Medline: 19980409

AB Current models of retroviral entry hypothesize that interactions between the viral envelope protein and the host receptor(s) induce conformational changes in the envelope protein that activate the envelope protein and initiate fusion. We employed a **liposome-binding** assay to demonstrate **directly** and characterize the activation of a model retroviral envelope protein (EnvA) from Rous sarcoma virus (RSV). In the presence of purified viral receptor, the trimeric ectodomain of

EnvA was converted from a water-soluble form to a membrane-associated form, consistent with conversion of the envelope protein to its fusogenic state. This activation was nonlinear with respect to receptor concentration, suggesting cooperativity within the trimeric envelope protein. The activated EnvA was stably associated with the target membrane through hydrophobic interactions, behaving like an intrinsic membrane protein. The ability of EnvA to associate with membrane was coincident with a loss of receptor-binding activity, suggesting that during viral entry activated EnvA dissociates from the receptor to facilitate membrane fusion. These results provide direct evidence that receptor binding triggers conversion of the EnvA protein to a membrane-binding form, illustrating that RSV is a useful model for the study of retroviral entry and activation of pH-independent fusion proteins.

L13 ANSWER 5 OF 26 MEDLINE on STN
ACCESSION NUMBER: 1998042437 MEDLINE
DOCUMENT NUMBER: 98042437 PubMed ID: 9375004
TITLE: Membrane fusion activity of Semliki Forest virus in a liposomal model system: specific inhibition by Zn2+ ions.
AUTHOR: Corver J; Bron R; Snippe H; Kraaijeveld C; Wilschut J
CORPORATE SOURCE: Department of Physiological Chemistry, GUIDE, University of Groningen, The Netherlands.
SOURCE: VIROLOGY, **(1997 Nov 10)** 238 (1) 14-21.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199712
ENTRY DATE: Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971215

AB Semliki Forest virus (SFV) has been shown previously to fuse efficiently with cholesterol- and sphingolipid-containing liposomal model membranes in a low-pH-dependent manner. Several steps can be distinguished in this process, including low-pH-induced irreversible binding of the virus to the **liposomes**, facilitated by **target** membrane cholesterol, and subsequent fusion of the viral membrane with the **liposomal** bilayer, specifically catalyzed by **target** membrane sphingolipid. Binding and fusion are mediated by the heterodimeric viral envelope **glycoprotein** E2/E1. At low pH the heterodimer dissociates, and the E1 monomers convert to a homotrimeric structure, the presumed fusion-active conformation of the viral spike. In this paper, we demonstrate that SFV-liposome fusion is specifically inhibited by Zn2+ ions. The inhibition is at the level of the fusion reaction itself, since virus-**liposome binding** was found to be unaffected. Zn2+ did not inhibit E2/E1 dissociation, but severely inhibited exposure of an acid-specific epitope on E1, E1 homotrimer formation, and acquisition of trypsin-resistance. It is concluded that virus--**liposome binding** solely requires low-pH-induced E2/E1 heterodimer dissociation, while fusion depends on further rearrangements in the E1 spike protein. As these rearrangements occur subsequent to the binding step, their precise course, including the formation of a fusion complex, may be influenced by interaction of E1 with target membrane lipids.

L13 ANSWER 6 OF 26 MEDLINE on STN
ACCESSION NUMBER: 96054974 MEDLINE
DOCUMENT NUMBER: 96054974 PubMed ID: 7590672
TITLE: Specific targeting of human hepatocellular carcinoma cells by immunoliposomes in vitro.
AUTHOR: Moradpour D; Compagnon B; Wilson B E; Nicolau C; Wands J R

CORPORATE SOURCE: Molecular Hepatology Laboratory, Massachusetts General Hospital Cancer Center, Harvard Medical School, Charlestown, USA.
CONTRACT NUMBER: AA-02666 (NIAAA)
AA-08169 (NIAAA)
CA-35711 (NCI)
SOURCE: HEPATOLOGY, **(1995 Nov)** 22 (5) 1527-37.
Journal code: 8302946. ISSN: 0270-9139.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951214

AB The monoclonal antibody AF-20 was raised against the human hepatocellular carcinoma (HCC) cell line FOCUS and binds with high affinity to a rapidly internalized 180-kd homodimeric **glycoprotein** that is abundantly expressed on the surface of human HCC and other human cancer cell lines. Immunoliposomes were produced by covalently coupling AF-20 to liposomes containing carboxyfluorescein. Interaction of immunoliposomes with various HCC cell lines in vitro was quantitatively assessed by flow cytometry and qualitatively analyzed by fluorescence microscopy. Liposomes bearing an isotype-matched nonrelevant monoclonal antibody (MAb) and cell lines not expressing AF-20 antigen served as controls. AF-20-immunoliposomes specifically bound to HCC and other human cancer cell lines expressing the AF-20 antigen and were rapidly internalized at 37 degrees C. Interaction of AF-20-**conjugated liposomes** with these cell lines was between 5 and 200 times greater than that of unconjugated liposomes, whereas no difference was observed between control liposomes bearing a nonrelevant antibody and unconjugated liposomes. Specificity of **liposome-target** cell interaction was confirmed by competitive inhibition assays. Kinetic analysis showed rapid association of AF-20 immunoliposomes with target cells, with saturation conditions being reached after 60 minutes. We conclude that the MAb AF-20 directs highly efficient, specific, and rapid targeting of immunoliposomes to human HCC and other human cancer cell lines in vitro. This targeted liposomal delivery system represents a promising approach for the development of immunotargeted diagnosis and therapy strategies against HCC.

L13 ANSWER 7 OF 26 MEDLINE on STN
ACCESSION NUMBER: 87049619 MEDLINE
DOCUMENT NUMBER: 87049619 PubMed ID: 3022792
TITLE: Target-sensitive immunoliposomes: preparation and characterization.
AUTHOR: Ho R J; Rouse B T; Huang L
CONTRACT NUMBER: CA00718 (NCI)
CA24553 (NCI)
EY05093 (NEI)
SOURCE: BIOCHEMISTRY, **(1986 Sep 23)** 25 (19) 5500-6.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198701
ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19980206
Entered Medline: 19870109

AB A novel target-sensitive immunoliposome was prepared and characterized. In this design, **target**-specific **binding** of

antibody-coated **liposomes** was sufficient to induce bilayer destabilization, resulting in a site-specific release of liposome contents. Unilamellar liposomes were prepared by using a small quantity of palmitoyl-immunoglobulin G (pIgG) to stabilize the bilayer phase of the unsaturated dioleoylphosphatidylethanolamine (PE) which by itself does not form stable liposomes. A mouse monoclonal IgG antibody to the **glycoprotein** D of Herpes simplex virus (HSV) and PE were used in this study. A minimal coupling stoichiometry of 2.2 palmitic acids per IgG was essential for the stabilization activity of pIgG. In addition, the minimal pIgG to PE molar ratio for stable liposomes was 2.5 X 10(-4). PE immunoliposomes bound with HSV-infected mouse L929 cells with an apparent Kd of 1.00 X 10(-8) M which was approximately the same as that of the native antibody. When 50 mM calcein was encapsulated in the PE immunoliposomes as an aqueous marker, **binding** of the **liposomes** to HSV-infected cells resulted in a cell concentration dependent lysis of the liposomes as detected by the release of the encapsulated calcein. Neither uninfected nor Sendai virus infected cells caused a significant amount of calcein release. Therefore, the release of calcein from PE immunoliposomes was target specific. Dioleoylphosphatidylcholine immunoliposomes were not lysed upon contact with infected cells under the same conditions, indicating that PE was essential for the **target**-specific **liposome** destabilization. (ABSTRACT TRUNCATED AT 250 WORDS)

L13 ANSWER 8 OF 26 MEDLINE on STN
ACCESSION NUMBER: 81077320 MEDLINE
DOCUMENT NUMBER: 81077320 PubMed ID: 6255476
TITLE: Antigen-**liposome** modification of **target** cells as a method to alter their susceptibility to lysis by cytotoxic T lymphocytes.
AUTHOR: Hale A H; Ruebush M J; Lyles D S; Harris D T
CONTRACT NUMBER: AI 00383 (NIAID)
AI 15785 (NIAID)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, **(1980 Oct)** 77 (10) 6105-8.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198102
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19970203
Entered Medline: 19810226

AB A method of liposome modification of cell surfaces to render unsuitable target cells susceptible to lysis by anti-viral cytotoxic T lymphocytes (CTLs) is described. Liposomes containing the hemagglutinin-neuraminidase (HN) and fusion (F) **glycoproteins** of Sendai virus as well as purified H-2Kk cells and rendering those cells susceptible to lysis by B10. A anti-Sendai virus or anti-H-2Kk CTLs. The absence from the modifying liposomes of the HN or F proteins or H-2Kk antigens eliminated the ability of the target cells to be recognized and lysed by either effector cell population. Vesicles containing HN, H-2Kk molecules, and inactive fusion protein (Fo) were not capable of increasing the susceptibility of h-2-negative target cells to lysis. Liposomes containing inactive fusion protein were similarly unable to render H-2-positive target cells susceptible to lysis by anti-Sendai virus CTLs, suggesting that fusion of the liposomes to the cell surface is a prerequisite to lysis. It did not appear that **attachement** of **liposomes** to the cell surface was sufficient for generation of susceptible targets, however, because attachment to the cell surface was observed, as long as the HN **glycoprotein** was present in the

liposomes. These results indicate that purified H-2Kk **glycoproteins** are target antigens for anti-H-2k CTLs and that B10 . A anti-Sendai virus CTLs recognize in an H-2-restricted manner the HN, F, or both **glycoproteins** of Sendai virus in the context of the purified H-2Kk **glycoproteins**. This technique of liposome modification of cell surfaces has potential applications in the examination of CTL antigen recognition and immunotherapy of many viral and neoplastic diseases.

L13 ANSWER 9 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:156721 BIOSIS
DOCUMENT NUMBER: PREV199799455924
TITLE: Enhanced gene delivery and expression in human hepatocellular carcinoma cells by cationic immunoliposomes.
AUTHOR(S): Compagnon, Beatrice; Moradpour, Darius; Alford, Dennis R.; Larsen, Charles E.; Stevenson, Michael J.; Mohr, Leonhard; Wands, Jack R.; Nicolau, Claude [Reprint author]
CORPORATE SOURCE: CBR Lab. Harvard Med. Sch., 1256 Soldiers Field Road, Boston, MA 02135, USA
SOURCE: Journal of Liposome Research, (1997) Vol. 7, No. 1, pp. 127-141.
ISSN: 0898-2104.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Apr 1997
Last Updated on STN: 15 Apr 1997

AB A targeted vector allowing enhanced gene transfer to human hepatocellular carcinoma (HCC-1) cells in vitro was developed using cationic **liposomes** covalently **conjugated** with the mAb AF-20. This high affinity antibody recognizes a rapidly internalized 180 kDa cell surface **glycoprotein** which is abundantly expressed on the surface of human HCC and other cancer cells. Quantitative **binding** analysis of **liposomes** with **target** cells by flow cytometry showed specific association of mAb-targeted liposomes with human HCC cells. Using mAb-targeted cationic liposomes containing 20% DOTAP, in the presence or absence of serum, gene expression in HuH-7 cells was enhanced up to 40-fold as compared to **liposomes** **conjugated** with an isotype-matched nonrelevant control antibody. Transfection specificity was not observed in AF-20. This study demonstrates that cationic liposome formulations a control cell line that does not express the antigen recognized by mAb in vitro gene delivery and expression in the presence or absence of serum.

L13 ANSWER 10 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1996:256368 BIOSIS
DOCUMENT NUMBER: PREV199698812497
TITLE: Effect of lipid composition in modulation of multidrug resistance (mdr) by doxorubicin encapsulated in liposomes.
AUTHOR(S): Briggs, K. E.; Cabanes, A.; Gokhale, P. C.; Rahman, A.
CORPORATE SOURCE: Dep. Radiol. Lab. Med., Georgetown Univ. Med. Cent., Washington, DC 20007, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1996) Vol. 37, No. 0, pp. 332.
Meeting Info.: 87th Annual Meeting of the American Association for Cancer Research. Washington, D.C., USA. April 20-24, 1996.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 May 1996
Last Updated on STN: 31 May 1996

L13 ANSWER 11 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1994:303843 BIOSIS
DOCUMENT NUMBER: PREV199497316843
TITLE: Clinical evaluation of liposome encapsulated doxorubicin and the modulation of multidrug resistance in cancer cells.
AUTHOR(S): Rahman, Aquilur [Reprint author]; Treat, Joseph; Thierry, Alain; Husain, Syed R. [Reprint author]; Dritschilo, Anatoly
CORPORATE SOURCE: Dep. Med., Div. Hematology, Univ. Pa., Philadelphia, PA 19104, USA
SOURCE: Journal of Liposome Research, (1994) Vol. 4, No. 1, pp. 167-192.
ISSN: 0898-2104.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Jul 1994
Last Updated on STN: 14 Jul 1994

AB Doxorubicin is the cornerstone of some widely used combination chemotherapy regimens because of its high anticancer activity in a number of human neoplasms. However, its clinical use is highly compromised because of treatment-limiting acute and chronic toxicities of which cardiotoxicity has the most debilitating effect. Our laboratories have demonstrated that liposome encapsulated doxorubicin (LED) provides important advantages in regards to the attenuation of cardiotoxicity in rodents by altering pharmacokinetics and pharmacodynamics of the drug, provides effective protection from immunotoxicity and maintains full therapeutic activity of the drug in liposomes. A Phase I clinical trial of LED in cancer patients has establish the maximum tolerated dose of 90 mg/m-2 with granulocytopenia being the major treatment-limiting toxicity. We have performed a Phase II trial of LED in 20 recurrent breast cancer patients at a dose of 75 mg/m-2 as an intravenous infusion every three weeks. Objective responses were observed in 9/20 patients of which 5 demonstrated a complete response. Hematologic toxicity with LED consisted of only grade 1-2 granulocytopenia in some patients, whereas gastrointestinal toxicity, mucositis and venous sclerosis were markedly reduced. Alopecia was complete in all patients. Twelve patients received cumulative LED doses of more than 400 mg/m-2 and 8 of them received doses of over 500 mg/m-2. Five of these patients were followed by endomyocardial biopsies and 4 of them were found to be Billingham Grade 0 whereas one of them had Billingham Grade I toxicity (cumulative dose of 750 mg/m-2). This Phase II trial demonstrates higher therapeutic efficacy of LED than free doxorubicin in recurrent breast cancer patients with strong indication of cardiotoxicity protection at doses of 500-800 mg/m-2. The emergence of tumor cells resistant to major classes of cytotoxic agents is a predominant obstacle in cancer treatment. This resistance is frequently related to the expression of a plasma membrane P-**glycoprotein** (pgp) of 170 Kd that is encoded by a family of MDR genes. Support for the involvement of pgp in MDR has been shown by transfection of sensitive cells with an expression vector containing full length cDNA of the MDR1 gene, which results in the appearance of pgp and the sensitive cells convert to the drug-resistant phenotype. Our studies demonstrate that LED modulates very effectively the MDR phenotype in LZ cells, a Chinese hamster cell line made resistant to doxorubicin and the cellular drug uptake was 2 to 3 fold higher with LED exposure than with free drug. This modulation of drug resistance and enhanced cellular drug uptake is effected by the **direct binding** of **liposomes** to pgp on the surfaces of MDR phenotype cells. LED completely inhibited the photoaffinity labeling of pgp by azidopine in membrane vesicles of HL-60/VCR cells and in KB-GSV2 cells transfected with human MDR gene. These studies demonstrate that LED has unique effectiveness in overcoming MDR phenotype in cancer cells and appears to be a potentially attractive modality of treatment of human cancers.

L13 ANSWER 12 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1992:458547 BIOSIS
DOCUMENT NUMBER: PREV199294099947; BA94:99947
TITLE: EFFECT OF COVALENT MODIFICATION ON THE BINDING OF CHOLERA TOXIN B SUBUNIT TO ILEAL BRUSH BORDER SURFACES.
AUTHOR(S): UWIERA R E [Reprint author]; ROMANCYIA D A; WONG J P; FORSYTH G W
CORPORATE SOURCE: VETERINARY PHYSIOLOGICAL SCIENCES, UNIV SASKATCHEWAN, SASKATOON, SASKATCHEWAN S7N 0W0, CAN
SOURCE: Analytical Biochemistry, (1992) Vol. 204, No. 2, pp. 244-249.
CODEN: ANBCA2. ISSN: 0003-2697.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 7 Oct 1992
Last Updated on STN: 7 Oct 1992

AB A competitive binding assay has been developed to determine how modifications to the B subunit of cholera toxin affect the binding affinity of the subunit for an ileal brush border membrane surface. The Ricinus communis120 agglutinin (RCA120) specifically binds to terminal .beta.-D-galactosyl residues such as those found in oligosaccharide side chains of **glycoproteins** and ganglioside GM1. Conditions were designed to produce binding competition between the B subunit of cholera toxin and the RCA120 agglutinin. Displacement of RCA120 from brush border surfaces was proportional to the concentration of B subunit added. This assay was used to study the effect of modification of B subunit on competitive binding affinity for the ileal brush border surface. The B subunit of cholera toxin was modified by coupling an average of five sulfhydryl groups to each B subunit molecule and by reaction of the SH-modified B subunit with liposomes containing a surface maleimide group attached to phosphatidylethanolamine. SH-modified B subunit was approximately 200-fold more effective than native B subunit in displacing lectin from brush border surfaces in the competitive binding assay. The enhanced binding activity was retained on covalent attachment of the modified B subunit to the liposome surface. We conclude that the B subunit of cholera toxin may be a useful targeting agent for **directing liposomes** to cell surfaces that contain a ganglioside GM1 ligand.

L13 ANSWER 13 OF 26 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 94070373 EMBASE
DOCUMENT NUMBER: 1994070373
TITLE: Carbohydrate-mediated liposomal targeting and drug delivery.
AUTHOR: Jones M.N.
CORPORATE SOURCE: Dept. Biochemistry and Mol. Biology, University of Manchester,Manchester M13 9PT, United Kingdom
SOURCE: Advanced Drug Delivery Reviews, (1994) 13/3 (215-250).
ISSN: 0169-409X CODEN: ADDREP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
016 Cancer
026 Immunology, Serology and Transplantation
027 Biophysics, Bioengineering and Medical Instrumentation
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English

SUMMARY LANGUAGE: English

AB The surface of the cell is rich in carbohydrate moieties attached to both membrane glycolipids and **glycoproteins**. These oligosaccharides constitute potential recognition sites for carbohydrate-mediated interactions between cells and drugs carriers bearing suitable site-**directing** molecules. **Liposomes** constitute a potentially valuable type of drug carrier. The ability to incorporate various site-**binding** molecules into the **liposomal** surface leads to a wide range of delivery systems based on carbohydrate-mediated interactions. In this review the types of recognition site on the surface of mammalian cells are considered with regard to both their chemical composition and the physical constraints which might effect their recognition by drug carriers with site-directing groups. Of particular current interest are the cell surface carbohydrate-binding proteins (lectins) which have yet to be fully exploited as recognition sites for carrier systems. Potential liposomal drug carriers have been considered under a range of headings: glycolipid-bearing, **glycoprotein** -bearing, virus spike **glycoprotein**-bearing (the so-called 'virosomes'), antibody-bearing immunoliposomes, lipopolysaccharide, polysaccharide-bearing and lectin-bearing. Examples of the applications of these various types of liposomes and their targeting to recognition sites on cells are reviewed. It is clear that while these systems could be of considerable value for the targeting of drugs, a great deal more work has been reported on the preparation, control and targeting of liposomal systems involving carbohydrate-mediated interactions than has been reported on their actual use for the delivery of specific drugs to cells. Carbohydrate-mediated drug delivery using liposomes is very sophisticated approach which will not be easy to exploit without very considerable investment. At present, much of the technology required to exploit carbohydrate-mediated interactions in drug delivery is available and future progress will depend on a determination to use this technology to develop drug-carrying liposomal system. The diversity of potential systems is large and the choice of liposomal system for targeting a drug to a particular cell type will have to be determined by balancing specificity of the liposomal carrier against ease of production.

L13 ANSWER 14 OF 26 EMBASE
on STN

ACCESSION NUMBER: 79101199 EMBASE
DOCUMENT NUMBER: 1979101199
TITLE: Binding of HLA antigen-containing liposomes to bacteria.
AUTHOR: Klareskog L.; Banck G.; Forsgren A.; Peterson P.A.
CORPORATE SOURCE: Dept. Cell Res., Biomed. Cent., Univ. Uppsala, Sweden
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1978) 75/12 (6197-6201).
CODEN: PNASA6
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 026 Immunology, Serology and Transplantation
004 Microbiology
051 Leprosy and other Mycobacterial Diseases
LANGUAGE: English

AB Highly purified, detergent-solubilized HLA-A and-B antigens and HLA-D antigens were separately incorporated into liposomes. Detergent-solubilized transplantation antigens, but not papain-solubilized antigens lacking the membrane-integrated portions of the molecules, were **bound** to the **liposomes**. A considerable portion of the **liposome-bound** antigens displayed accessible antigenic sites, suggesting that they were oriented in the right-side-out **direction**. **Liposomes** containing the HLA-A and -B antigens or the HLA-D antigen interacted similarly with bacteria. The two types of **liposomes bound** efficiently to two strains of Neisseria catarrhalis (now classified as Branhamella catarrhalis) and to

one strain of Haemophilus influenzae, weakly to one strain of Escherichia coli, and not at all to another strain of E. coli. The binding between the HLA antigen-containing liposomes and one strain of N. catarrhalis was abolished when Fab fragments directed against the heavy chains of HLA-A and -B antigens or against HLA-D antigens, respectively, were added. In contrast Fab fragments against .beta.2-microglobulin did not measurably impede the bacteria-liposome interaction, suggesting that, with regard to the HLA-A and -B antigens, the heavy, but not the light, chains interacted with the bacteria. Additional experiments showed that N. catarrhalis preferentially interacted with transplantation antigens when mixed with detergent-solubilized lymphocyte membrane **glycoproteins**. These data suggest the HLA-A and -B and HLA-D antigens may have the function of interacting with foreign antigens such as bacteria.

L13 ANSWER 15 OF 26 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 130:149951 CA
TITLE: Coat assembly directs v-SNARE concentration into synthetic COPII vesicles
AUTHOR(S): Matsuoka, Ken; Morimitsu, Yasujiro; Uchida, Koji; Schekman, Randy
CORPORATE SOURCE: Department of Molecular and Cell Biology, Howard Hughes Medical Institute, University of California, Berkeley, Berkeley, CA, 94720, USA
SOURCE: Molecular Cell (**1998**), 2(5), 703-708
CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB COPII proteins are required to create transport vesicles and to select cargo mols. for transit from the ER. A reconstituted liposome budding reaction was used to detect the capture and concn. of membrane-assocd. v-SNARE mols. into synthetic COPII vesicles. A novel glutathione-phosphatidylethanolamine conjugate (Glut-PE) was synthesized and incorporated into chem. defined **liposomes** to provide **binding** sites for GST hybrid proteins. Large **liposomes** contg. **bound** cytoplasmic domains of the v-SNAREs, Sec22p or Bos1p, or of the ER resident proteins, Sec12p and Ufe1p, were exposed to COPII proteins and GMP-PNP. V-SNAREs but not resident proteins were concd. in synthetic COPII vesicles generated from donor liposomes. We conclude that COPII proteins are necessary and sufficient for cargo selection and vesicle morphogenesis.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 26 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 125:192364 CA
TITLE: Mechanisms of mutations inhibiting fusion and infection by Semliki Forest virus
AUTHOR(S): Kielian, Margaret; Klimjack, Matthew R.; Ghosh, Swati; Duffus, Wayne A.
CORPORATE SOURCE: Dep. Cell Biology, Albert Einstein College Med., Bronx, NY, 10461, USA
SOURCE: Journal of Cell Biology (**1996**), 134(4), 863-872
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Semliki Forest virus (SFV) infects cells by an acid-dependent membrane fusion reaction catalyzed by the virus spike protein, a complex contg. E1 and E2 transmembrane subunits. E1 carries the putative virus fusion peptide, and mutations in this domain of the spike protein were previously shown to shift the pH threshold of cell-cell fusion (G91A), or block

cell-cell fusion (G91D). We have used an SFV infectious clone to characterize virus particles contg. these mutations. In keeping with the previous spike protein results, G91A virus showed limited secondary infection and an acid-shifted fusion threshold, while G91D virus was noninfectious and inactive in both cell-cell and virus-liposome fusion assays. During the low pH-induced SFV fusion reaction, the E1 subunit exposes new epitopes for monoclonal antibody (mAb) binding and forms an SDS-resistant homotrimer, the virus assocs. hydrophobically with the target membrane, and fusion of the virus and target membranes occurs. After low pH treatment, G91A spike proteins were shown to bind conformation-specific mAbs, assoc. with **target liposome** membranes, and form the E1 homotrimer. However, both G91A membrane assocn. and homotrimer formation had an acid-shifted pH threshold and reduced efficiency compared to wt virus. In contrast, studies of the fusion-defective G91D mutant showed that the virus efficiently reacted with low pH as assayed by mAb **binding** and **liposome** assocn., but was essentially inactive in homotrimer formation. These results suggest that the G91D mutant is noninfectious due to a block in a late step in membrane fusion, sep. from the initial reaction to low pH and interaction with the target membrane, and involving the lack of efficient formation of the E1 homotrimer.

L13 ANSWER 17 OF 26 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 123:74303 CA
TITLE: Characterization of organ-specific immunoliposomes for delivery of 3',5'-O-dipalmitoyl-5-fluoro-2'-deoxyuridine in a mouse lung-metastasis model
AUTHOR(S): Mori, Atsuhide; Kennel, Stephen J.; Waalkes, Marjan van Borssum; Scherphof, Gerrit L.; Huang, Leaf
CORPORATE SOURCE: Department Pharmacology, University Pittsburgh School Medicine, Pittsburgh, PA, 15261, USA
SOURCE: Cancer Chemotherapy and Pharmacology (**1995**), 35(6), 447-56
CODEN: CCPHDZ; ISSN: 0344-5704
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A previous study has shown that lipophilic prodrugs can be delivered efficiently to normal lung endothelium by incorporation into **liposomes** covalently **conjugated** to monoclonal antibody (mAb) 34A against the lung endothelial anticoagulant protein thrombomodulin. In the present study, the potential use of these lung-targeted immunoliposomes (34A-liposomes) for delivery of a lipophilic prodrug, 3',5'-O-dipalmitoyl-5-fluoro-2'-deoxyuridine (dpFUdR), to the tumor-bearing lung was examd. using BALB/c mice bearing exptl. lung metastasis induced by i.v. injection of EMT-6 mouse mammary tumor cells. Immunohistochem. examn. of the tumor-bearing lung showed specificity of mAb 34A to lung endothelium. Tumor cells appeared to localize just outside of the normal blood vessels and were within a small diffusion distance from the mAb-binding sites. 111In-labeled 34A-liposomes contg. monosialoganglioside (GM1) were prepd. that included [3H]-dpFUdR at 3.0 mol% in the lipid mixt. In vitro cell binding studies further demonstrated that 34A-**liposomes bound** specifically to normal mouse lung cells that expressed thrombomodulin but not to EMT-6 cells. Biodistribution study showed efficient and immunospecific accumulation [3H]-dpFUdR incorporated into 34A-liposomes in the lung at a level parallel with that of 111In-labeled 34A-liposomes, indicating that the drug is delivered to the **target** organ in intact **liposomes**. Liposomal dpFUdR appeared to be metabolized in the lung to the parent drug FUdR at a rate slower than in the liver and spleen. Furthermore, treatment of lung-metastasis-bearing mice with dpFUdR incorporated into 34A-liposomes on days 1 and 3 after tumor cell injection resulted in a significant increase in the median survival time of treated mice as compared with control mice (%T/C value, 165%). DpFUdR

either dispersed in emulsion or incorporated into antibody-free liposomes was ineffective in prolonging the survival of mice. These results indicate the potential effectiveness of organ-specific immunoliposomes contg. a lipophilic prodrug for the targeted therapy of metastatic tumors.

L13 ANSWER 18 OF 26 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 122:89249 CA
TITLE: Adhesion molecules: a new target for immunoliposome-mediated drug delivery
AUTHOR(S): Bloemen, P. G. M.; Henricks, P. A. J.; van Bloois, L.; van den Tweel, M. C.; Bloem, A. C.; Nijkamp, F. P.; Crommelin, D. J. A.; Storm, G.
CORPORATE SOURCE: Department of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, PO Box 80.082, TB Utrecht, 3508, Neth.
SOURCE: FEBS Letters (**1995**), 357(2), 140-4
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The anti-ICAM-1 monoclonal antibody F10.2 was **conjugated** to **liposomes** to **target** to cells expressing the cell adhesion mol. ICAM-1. The authors demonstrate that F10.2 immunoliposomes bind to human bronchial epithelial cells (BEAS-2B) and human umbilical vein endothelial cells (HUVEC) in a specific, dose- and time-dependent manner. It appears that the degree of ICAM-1 expression is the limiting factor in the degree of immunoliposome binding to the cells. These results are a first step in the strategy for specific drug delivery to target sites characterized by increased expression of adhesion mols.

L13 ANSWER 19 OF 26 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 122:76029 CA
TITLE: Direct and biochemically functional detection of retrovirus in biological samples
INVENTOR(S): Faff, Ortwin
PATENT ASSIGNEE(S): Germany
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9428115	A1	19941208	WO 1994-DE610	19940531 <--
W: AU, BR, CA, CN, JP, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 4416300	A1	19941208	DE 1994-4416300	19940509 <--
DE 4416300	C2	19970410		
AU 9467933	A1	19941220	AU 1994-67933	19940531 <--
EP 707635	A1	19960424	EP 1994-916144	19940531 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE				
JP 08510136	T2	19961029	JP 1994-500112	19940531 <--
US 6268123	B1	20010731	US 1996-557108	19960228 <--

PRIORITY APPLN. INFO.: DE 1993-4318229 A 19930601
DE 1994-4416300 A 19940509
WO 1994-DE610 W 19940531

AB Structure-specific extn. with immobilized ligands directed against the viral surface is combined with function-specific retrovirus enzyme reactions (reverse transcriptase, RNase H, integrase, or protease) for diagnosis, monitoring and treatment of viral diseases, in transfusion and transplantation medicine, in virol. research and development, and for the

biol. quality control of pharmaceutical and biotechnol. products. Reverse transcription by reverse transcriptase, using retroviral RNA as template and tRNA as primer, is particularly suitable for the retrovirus-specific enzyme reaction. The newly synthesized cDNA products are identified by radioactive, photometric, luminescent, or fluorescent processes. This process represents a biochem. simulation of the natural process of retroviral infection and development within the cell (reverse transcription, integration, maturation) and allows several retroviral components (surface **glycoproteins**, enzymes, structural proteins, RNA and tRNA) to be simultaneously detected. The process takes 1-2 days; it may be easily and routinely carried out in a microtiter format and thus allows many probes to be processed simultaneously within a short time. In addn., the process may be universally applied to all species of retrovirus by corresponding specific ligands. Thus, wells of a microtiter plate were coated with antibodies to T47D retroviral particles and incubated successively with (a) a virus-contg. sample and (b) a buffered lysis-reaction mixt. contg. DTT, EDTA, deoxyribonucleoside triphosphates, dUTP-biotin, and dUTP-digoxigenin. The reaction mixt. was then transferred to a streptavidin-coated microtiter plate and the immobilized cDNA was detected by incubation with peroxidase-labeled anti-digoxigenin antibody and ABTS (peroxidase substrate).

L13 ANSWER 20 OF 26 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 114:150209 CA
TITLE: Preparation and characterization of target-sensitive immunoliposomes
INVENTOR(S): Huang, Leaf
PATENT ASSIGNEE(S): University of Tennessee Research Corp., USA
SOURCE: U.S., 20 pp. Cont.-in-part of U.S. Ser. No. 816,817, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
US 4957735	A	19900918	US 1987-12321	19870209	<--
US 4708933	A	19871124	US 1984-619844	19840612	<--
WO 8704795	A1	19870813	WO 1987-US222	19870123	<--
W: BR, JP					
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE					
EP 258388	A1	19880309	EP 1987-901814	19870123	<--
R: BE, DE, FR, GB, IT, SE					
JP 01500848	T2	19890323	JP 1987-501616	19870123	<--

PRIORITY APPLN. INFO.:

US 1984-619844	19840612
US 1986-816817	19860107
EP 1985-903151	19850611
WO 1987-US222	19870123

AB **Target**-specific **binding** of antibody-coated **liposomes** is sufficient to induce bilayer destabilization, resulting in a site-specific release of liposome contents. Unilamellar liposomes are prepd. by using a small quantity of palmitoyl IgG to stabilize the unsatd. phosphatidylethanolamine (PE) which by itself does not form stable liposomes. A mouse monoclonal IgG antibody to **glycoprotein** D of herpes simplex virus (HSV) and dioleoyl PE were used in 1 preferred embodiment. In another preferred embodiment, potentially cytotoxic antiviral drugs were entrapped in target-sensitive immunoliposomes and delivered to HSV-infected cells. Potency was .apprx.1000 times superior to the free drug and cytotoxicity was reduced .apprx.3000-fold.

L13 ANSWER 21 OF 26 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 112:84054 CA
TITLE: Interactions of human lymphoblasts with targeted vesicles containing Sendai virus envelope proteins
AUTHOR(S): Sechoy, O.; Vidal, M.; Philippot, J. R.; Bienvenue, A.
CORPORATE SOURCE: INSERM, Montpellier, 34100, Fr.
SOURCE: Experimental Cell Research (**1989**), 185(1), 122-31
CODEN: ECREAL; ISSN: 0014-4827
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The internalization of targeted fusogenic liposome content to leukemic T cells (CEM) was studied in vitro. A method is described for the covalent coupling of T101 antibody to the surface of liposomes ands the incorporation of fusogenic viral protein into the liposome membrane. Hygromycin B, an impermeant inhibitor of protein synthesis, was encapsulated in the targeted fusogenic **liposomes** and delivered **directly** to the cytoplasm of leukemic T cells by fusion between the 2 membranes. The cytotoxic effect was measured by [3H]thymidine incorporation. CEM are rapidly and specifically killed by the drug encapsulated in the targeted fusogenic liposomes. This effect is due to the **binding** of the **liposome** by means of the antibody and then to the fusion of the liposome with the targeted cell membrane, mediated by F protein.

L13 ANSWER 22 OF 26 CA COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 108:43888 CA
TITLE: Kinetic and ultrastructural studies of interactions of target-sensitive immunoliposomes with herpes simplex virus
AUTHOR(S): Ho, Rodney J. Y.; Ting-Beall, H. P.; Rouse, Barry T.; Huang, Leaf
CORPORATE SOURCE: Dep. Biochem., Univ. Tennessee, Knoxville, TN, 37996-0840, USA
SOURCE: Biochemistry (**1988**), 27(1), 500-6
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The bilayer phase of dioleoyl phosphatidylethanolamine (DOPE) can be stabilized with palmitoyl-IgG monoclonal antibody to the **glycoprotein** gD of the Herpes Simplex Virus (HSV). Interactions of DOPE immunoliposomes with the target virions were characterized by analyzing the kinetics of lipid mixing, liposomal content release, and by ultrastructural studies. As revealed by a resonance energy transfer assay, lipid mixing between PE immunoliposomes and virions was very rapid, with a second-order rate const. (kapp) of 0.173 (min)-1 (.mu.g/mL virus)-1. In comparison, content release from DOPE immunoliposomes was much slower and exhibited multiple-phase, mixed-order kinetics, indicating that liposome destabilization involved fusion of liposomes with HSV. The extent and the apparent rate of liposome destabilization were strongly dependent on liposome concn. This was evident by the fact that only 1 to 2 liposomes were destabilized by each virus particle at low liposome concn. (0.1 .mu.M). For higher liposome concns. (1-10 .mu.M), this value was 35-104. This finding implies that collision among the virus-**bound liposomes** is essential for the eventual collapse of DOPE immunoliposomes to form the hexagonal (HII) equil. phase which was obsd. using freeze-fracture electron microscopy. Studies employing sol. gD, immobilized on latex beads, indicated that a multivalent antigen source is essential for DOPE immunoliposome destabilization. Immediately after **liposome**-virus **binding**, fusion of **liposome** with the viral membrane then follows. Upon growth of the fusion complexes, which increase to 35-104 liposomes for each virus, an eventual collapse of the structure results, driving PE to its equil.

structure of HII phase.

L13 ANSWER 23 OF 26 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 97:911383 SCISEARCH
THE GENUINE ARTICLE: YJ695
TITLE: Use of circular dichroism spectroscopy in determining the conformation of a monoclonal antibody prior to its incorporation in an immunoliposome
AUTHOR: Ng K Y (Reprint); Zhao L M; Meyer J D; RittmannGrauer L; Manning M C
CORPORATE SOURCE: UNIV COLORADO, HLTH SCI CTR, SCH PHARM, DEPT PHARMACEUT SCI, CAMPUS BOX C-238, 4200 E 9TH AVE, DENVER, CO 80262 (Reprint); HYBRITECH INC, SAN DIEGO, CA 92121
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS, (**NOV 1997**) Vol. 16, No. 3, pp. 507-513.
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD, ENGLAND OX5 1GB.
ISSN: 0731-7085.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 23

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Attachment** of antibodies to **liposomes** endows **target** specificity to **liposomes** for a certain cell or organ that express the targeted antigenic determinant. These so-called immunoliposomes hold high promise as targeted drug carriers. One approach of immunoliposome preparation involves conjugating antibodies to hydrophobic anchors (e.g. fatty acids or phospholipid molecules) for incorporation into the **liposome** membrane. Often, these **conjugation** reactions are harsh and may result in undesirable chemical and structural changes in the antibody molecule. This necessitates confirmation of the target specificity of the derivatized antibody prior to its incorporation into the liposome. Our approach to this problem is to utilize circular dichroism spectroscopy, which can detect subtle structural differences in proteins with high reproducibility and accuracy in relatively short period of time. In addition, circular dichroism is a non-destructive technique. In this study, we demonstrate the ability of circular dichroism to confirm the conformation of a model antibody, HYB-241, conjugated to N-glutarylphosphatidylethanolamine, prior to its mixing with dioleoylphosphatidylethanolamine/dioleoylphosphatidic acid to form a target-sensitive immunoliposome. (C) 1997 Elsevier Science B.V.

L13 ANSWER 24 OF 26 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 96:789665 SCISEARCH
THE GENUINE ARTICLE: VP322
TITLE: TARGETING OF LIPOSOMES TO HIV-1-INFECTED CELLS BY PEPTIDES DERIVED FROM THE CD4 RECEPTOR
AUTHOR: SLEPUSHKIN V A; SALEM I I; ANDREEV S M; DAZIN P; DUZGUNES N (Reprint)
CORPORATE SOURCE: UNIV PACIFIC, SCH DENT, DEPT MICROBIOL, 2155 WEBSTER ST, SAN FRANCISCO, CA, 94115 (Reprint); UNIV PACIFIC, SCH DENT, DEPT MICROBIOL, SAN FRANCISCO, CA, 94115; DI IVANOVSKII INST VIROL, MOSCOW 123098, RUSSIA; UNIV GRANADA, DEPT PHARMACEUT TECHNOL, GRANADA 18071, SPAIN; INST IMMUNOL, MOSCOW, RUSSIA; UNIV CALIF SAN FRANCISCO, HOWARD HUGHES MED INST, SAN FRANCISCO, CA, 94143; UNIV CALIF SAN FRANCISCO, DEPT BIOPHARMACEUT SCI, SAN FRANCISCO, CA, 94143
COUNTRY OF AUTHOR: USA; RUSSIA; SPAIN
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (

23 OCT 1996) Vol. 227, No. 3, pp. 827-833.
ISSN: 0006-291X.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 26

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Liposomes can be targeted to HIV-infected cells by either reconstituting transmembrane CD4 in the membrane or covalently coupling soluble CD4 to modified lipids. We investigated whether synthetic peptides could be used as ligands for targeting liposomes. A synthetic peptide from the complementarity determining region 2 (CDR-2)-like domain of CD4 could bind specifically to HIV-infected cells and mediate the **binding** of peptide-coupled **liposomes** to these cells. A peptide from the CDR-3-like domain of CD4 inhibited HIV-induced syncytia formation, but failed to **target liposomes** to infected cells. This apparent discrepancy may be due to the requirement for a conformational change in the CD4 receptor for the CDR-3 region to interact with the HIV envelope protein. Our results demonstrate the feasibility of using synthetic peptides to **target liposomes** containing antiviral drugs to HIV-infected cells. (C) 1996 Academic Press, Inc.

L13 ANSWER 25 OF 26 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 95:138542 SCISEARCH
THE GENUINE ARTICLE: QG848
TITLE: INFLUENZA HEMAGGLUTININ-MEDIATED MEMBRANE-FUSION - INFLUENCE OF RECEPTOR-BINDING ON THE LAG PHASE PRECEDING FUSION
AUTHOR: STEGMANN T (Reprint); BARTOLDUS I; ZUMBRUNN J
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SOURCE: BIOCHEMISTRY, (**14 FEB 1995**) Vol. 34, No. 6, pp. 1825-1832.
ISSN: 0006-2960.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 39

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Fusion of influenza virus with liposomes is triggered by low pH, resulting in a conformational change in the fusion protein (HA) and-the insertion of fusion peptides, from HA into the Liposomal membrane. Fusion does not take place immediately after insertion but is preceded by a lag phase, the duration of which, as we have found previously, depends on the presence of ganglioside receptors in the liposomal membrane [Stegmann, T., White, J. M., and Helenius, A. (1990) EMBO J. 9, 4231-4241]. Here we have investigated why that is the case. Surprisingly, the 2-4-fold shorter lag phase observed with phosphatidylcholine (PC)/phosphatidylethanolamine (PE)/ganglioside liposomes was ndt due to slower or more readily reversible binding of the virus to PC/PE liposomes lacking receptors. Nevertheless, using **liposomes** with various glycolipids as **targets**, it was found that specific HA-receptor interactions were required for a shorter lag, and not just the negative charge of the gangliosides, or the presence of ceramide lipid tails in the **Liposomal** membrane. Receptor **binding** also,did not facilitate the conformational change in HA. Surprisingly, however, it was found that after an incubation of the virus at low pH in the absence of target membranes at 0 degrees C for several minutes, the binding and fusion activity of virus using PC/PE liposomes, but not PC/PE/ganglioside **Liposomes** as **targets**, was decreased. The population of virus that did still bind to and fuse with the PC/PE liposomes after low pH preincubation did so after a significantly increased lag time.

Binding of virus to **Liposomes** without receptors is solely due to insertion of viral fusion peptides into the liposomal membrane, suggesting that the availability of fusion peptides is decreased after low pH preincubation. Zn accordance with this suggestion, if the Liposomal Lipid bilayers were in the gel phase, binding of virus to PC liposomes but not to PC/ganglioside liposomes was strongly inhibited, and the lag phase was about 9 times shorter for liposomes with receptors. Therefore, these results suggest that ganglioside receptors shorten the lag phase because they facilitate insertion of fusion peptides into the target membrane.

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ACCESSION NUMBER: 91:5869 SCISEARCH
THE GENUINE ARTICLE: EN921
TITLE: INTERMEDIATES IN INFLUENZA INDUCED MEMBRANE-FUSION
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SOURCE: EMBO JOURNAL, (**1990**) Vol. 9, No. 13, pp. 4231-4241.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 47

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Our results show that the mechanism by which influenza virus fuses with target membranes involves sequential complex changes in the hemagglutinin (HA, the viral fusion protein) and in the contact site between virus and target membrane. To render individual steps amenable to study, we worked at 0-degrees-C which decreased the rate of fusion and increased the efficiency. The mechanism of fusion at 0-degrees-C and 37-degrees-C was similar. The process began with a conformational change in HA which exposed the fusion peptides but did not lead to dissociation of the tops of the ectodomain of the trimer. The change in the protein led to immediate hydrophobic attachment of the virus to the **target liposomes**. **Attachment** was followed by a lag period (4-8 min at 0-degrees-C, 0.6-2 s at 37-degrees-C) during which rearrangements occurred in the site of membrane contact between the virus and liposome. After a further series of changes the final bilayer merger took place. This final fusion event was not pH dependent. At 0-degrees-C efficient fusion occurred without dissociation of the top domains of the HA trimer, suggesting that a transient conformation of HA is responsible for fusion at physiological temperatures. The observations lead to a revised model for HA mediated fusion.